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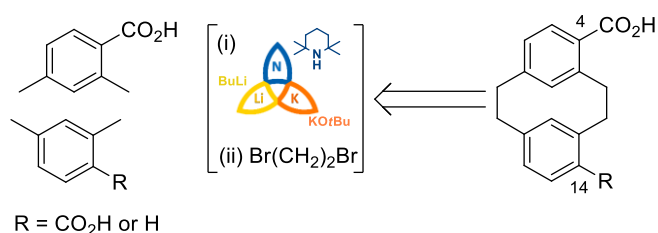
# Synthesis, Separation and Structural Analysis of Planar Chiral Carboxy Substituted [2.2]metaCyclophanes

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## Abstract



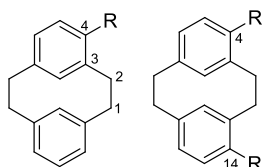
A two step synthesis of carboxy functionalized planar chiral [2.2]metacyclophanes from *m*-xylenes is described. Both transformative steps utilize LiNK metalation conditions (BuLi, KOtBu, TMP(H)) for *m*-xylene benzylic deprotonation with subsequent *in situ* oxidative C-C coupling. Inclusion of the carboxy substituents at either C4 or C4 and C14 renders the [2.2]metacyclophanes planar chiral and the structural analysis of both substitution patterns has been achieved with X-ray crystallography and NMR. The C4 mono and C4/14 di-substituted carboxylic acid methyl ester racemates were readily separated by analytical and preparative chiral HPLC and their inversion barriers measured in heptanes at 373 K are 32.3 kcal/mol and 31.1 kcal/mol respectively. The facile synthesis, separation and sufficiently high inversion barriers of the [2.2]metacyclophane planar chiral class warrant their investigation as potential planar chiral catalysts and ligands which to date has yet to be explored.

## Introduction

The unique and intriguing properties of constrained [2.2]cyclophanes has lead to a continued interest in them since the first report of Brown and Farthing in 1949.<sup>1</sup> “Phane” molecules combine the interactions between layered  $\pi$ -systems within constrained three-dimensional architecture, and this unique feature has been extensively exploited and developed leading to a widely variable class of chiral molecules successfully employed in stereoselective synthesis.<sup>2</sup> In this context the *para*-[2.2]paracyclophanes have seen a recent resurgence of interest notably as planar chiral scaffolds for asymmetric catalysis.<sup>3</sup> Among the other potential chiral cyclophane structures, the planar chirality of [2.2]metacyclophanes has received scant attention, with the synthesis of only a few chiral derivatives haven been described.<sup>4</sup> Thermodynamic and kinetics studies have shown that for the [*n.n*]metacyclophanes, only the most constrained [2.2]metacyclophanes have an inversion barrier (torsional barrier) high enough to permit resolution of conformationally stable enantiomers.<sup>5</sup> However, only few examples of optical resolution<sup>4a,6</sup> and crystal structure determinations<sup>7</sup> of planar chiral [2.2]metacyclophanes have been reported to date.

We recently reported that challenging benzylic metalations can be achieved with excellent regioselectivity by means of the mixed Li/K metal TMP amide (LiNK metalation conditions) generated *in situ* by the reagent triad BuLi/KOt-Bu/TMP(H).<sup>8</sup> In the course of our studies aimed to exploit further synthetic applications of LiNK metalation conditions, we described a new two-step general approach to [2.2]metacyclophanes starting from cheap commercially available substituted *m*-xylenes.<sup>9</sup> Our strategy employs a selective benzylic metalation with an *in situ* oxidative coupling reaction<sup>10</sup> for both synthetic operations under LiNK metalation conditions. The synthetic usefulness of this approach prompted us to expand our approach to the synthesis of planar chiral [2.2]cyclophane derivatives. In order to render the [2.2]metacyclophane scaffold planar chiral, the symmetry plane bisecting the cyclophane ring must be differentiated by substitution in either

positions C-4 or C-4 and C-14 (Figure 1), which renders the original  $C_2$  symmetry lost and planar chirality is created. In this report the synthesis, structural characterization, enantiomer separation and stability analyses of potentially useful optically active mono- and di-carboxy[2.2]metacyclophanes are described.

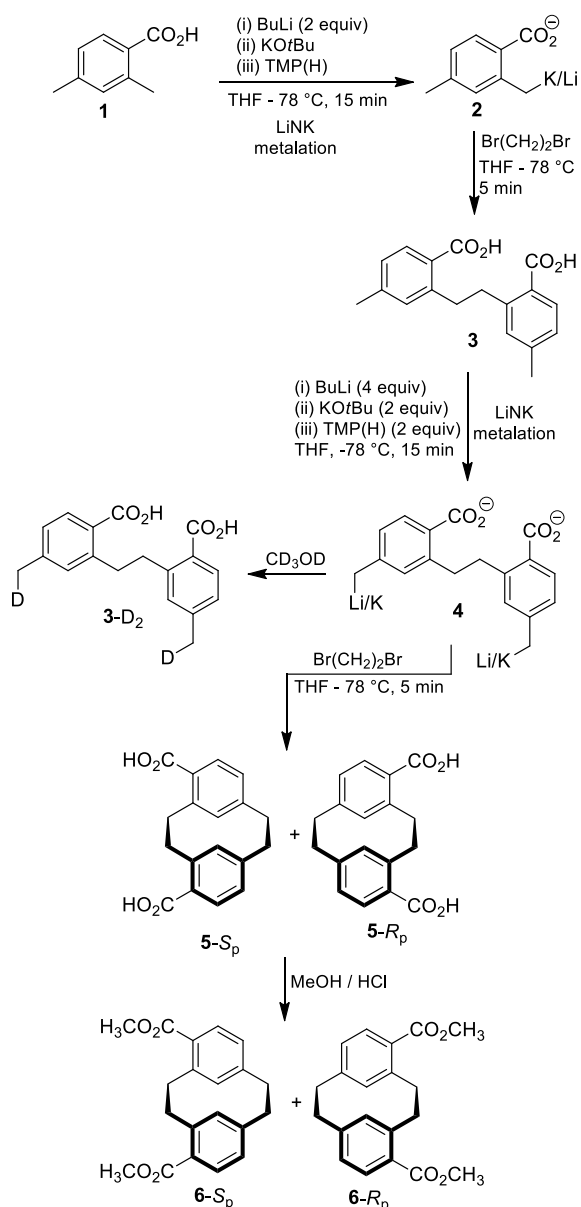


**Figure 1.** Planar Chiral [2.2]metacyclophanes

## Results and Discussion

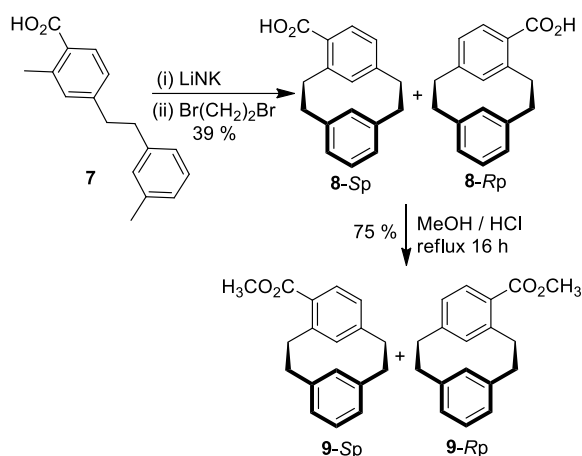
The preparation of planar chiral carboxy[2.2]metacyclophanes derivatives has already been described in the literature resorting to multi-steps synthetic approaches. The synthesis of [2.2]metacyclophane-4,14-dicarboxylic acid **5** has been previously accomplished by conversion of the corresponding dimethyl derivative, which has been obtained as a mixture with the 4,12- isomer after stereoselective chloromethylation of toluene followed by Wurtz coupling.<sup>11</sup> Bromomethylation and subsequent Sommelet reaction led to the corresponding dialdehyde derivative which has been finally oxidized to the target compound **5**.<sup>11</sup> Similarly, the monosubstituted 4-carboxylic acid **8** has been prepared by an elaborated 7-steps synthesis.<sup>4a</sup> In this case, the metacyclophane skeleton was built by alkylation of lithiated isophthalaldehyde bis-dithiane with 1-bromo-2,4-dibromobenzene followed by reductive cleavage of dithiane with Raney Ni catalyst. Treatment of the resulting 4-bromo[2.2]metacyclophane with diazomethane followed by basic hydrolysis led to the corresponding carboxylic acid **8**. Both mono- and bis-carboxy racemic mixtures of **5** and **8** were resolved via their diastereomeric salts with (+)-1-phenylethylamine.<sup>4a,12</sup>

LiNK metalation conditions with in situ oxidative coupling offers a facile general approach to the [2.2]metacyclophanes.<sup>9</sup> Using this strategy access to carboxy substituted planar chiral derivatives is possible from the two inexpensive starting material *m*-xylene and 2,4-dimethylbenzoic acid. Using these two reagents the planar chiral C-4 carboxy and C-4/14 di-carboxy substituted derivatives could be synthesized which could viewed as bench mark examples of this planar chiral scaffold. On the basis of our previously reported results on the thermodynamically controlled selective metalation of 2,4-dimethylbenzoic acid **1** under LiNK conditions (90% D incorporation in the more acidic 2-position),<sup>9</sup> a two step metalation/coupling sequence to achieve the desired [2.2]metacyclophane-4,14-dicarboxylic acid **5** was carried out (Scheme 1). Treatment of **1** with 2 equivalents of BuLi (one for the deprotonation of the carboxylic group) and 1 equivalent of KO*t*-Bu and TMP(H) in THF at -78 °C for 15 min led to the dianion **2**, which underwent oxidative homocoupling after addition of 1,2-dibromoethane at -78 °C leading to the corresponding 2,2'-(ethane-1,2-diyl)bis(4-methylbenzoic acid) **3** in 82% yield. In order to assess the di-benzylic metalation of **3** a deuteration study was first carried out prior to attempting the cyclophane formation via ring closure step. The resulting homo-dimer product represented a challenging substrate for a subsequent benzylic di-metalation due to the formation of a tetra-anionic intermediate **4**. Upon metalation of **3** with LiNK conditions of 4:2:2 equivalences of BuLi:KO*t*-Bu:TMP(H) at -78 °C for 15 min and quenching with CD<sub>3</sub>OD, <sup>2</sup>H NMR showed that selective deuterium incorporation into both benzylic positions had been achieved to give **3**-D<sub>2</sub> without any aryl deuteration detected. To effect ring closure to the cyclophane metalation was repeated to provide the tetra-anion **4** which was oxidatively ring closed with 1,2-dibromoethane leading to **5<sub>rac</sub>** in 35% yield after purification. The product was subsequently converted to the corresponding [2.2]metacyclophane-4,14-dicarboxylic acid dimethyl ester **6<sub>rac</sub>** with MeOH/HCl which was isolated pure following column chromatography.



**Scheme 1:** Iterative LiNK/oxidative coupling synthesis of [2.2]metacyclophane-4,14-dicarboxylic acid **5** and corresponding dimethyl ester **6**.

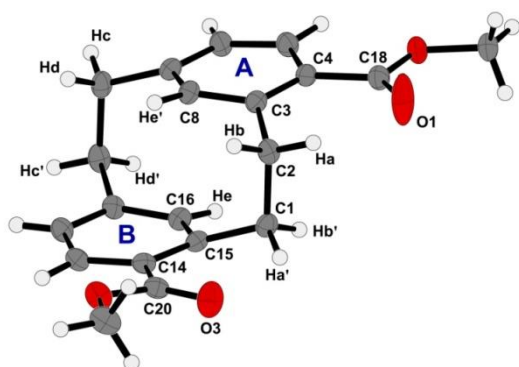
In a similar way, we have previously shown that LiNK di-benzylic metalation of substrate **7** and oxidative ring closure generates the planar chiral 4-carboxylic acid substituted metacyclophane **8** (Scheme 2).<sup>9</sup> Purification of the crude reaction mixture was easily achieved by column chromatography giving **8** in 39% yield as a racemic mixture. Esterification of carboxylic acid **8<sub>rac</sub>** was carried out in MeOH/HCl under reflux to provide cyclophane **9<sub>rac</sub>** in a quantitative yield.



**Scheme 2:** LiNK / oxidative coupling synthesis of 4-carboxy-[2.2]metacyclophanes **8** and **9**.

In anticipation of future investigations into the ability of metacyclophanes to act as chiral catalysts and ligands efforts were made to obtain solid state structures and high resolution NMR data for **6**, **8** and **9** as little of such data has been previously reported. Metacyclophane **6** was crystallized by the slow room temperature evaporation of a diethyl ether solution into the orthorhombic space group *Pna*2<sub>1</sub>,<sup>13</sup> and analysis of the X-ray crystal structure with characteristic <sup>1</sup>H NMR data collected at 500 MHz are summarized in Table 1.

**Table 1:** Crystal Structure and relevant NMR data for **6**



Entry	Measurement	Data
1	Intra-annular distance (C8 to C16)	2.66(1) Å
2	A ring distortion from planarity	7.7(1)°



3	B ring distortion from planarity	7.7(4)°
4	Bond length C1-C2	1.574(2) Å
5	Angle C1-C2-C3	109.94(12)°
6	Torsion angle C3-C4-C18-O1	−2.2(3)°
7	Torsion angle C15-C14-C20-O3	−9.5(2)°
8	Ha/Ha' chemical shift <sup>a</sup>	4.27 ppm
9	Hb/Hb' chemical shift <sup>a</sup>	1.96 ppm
10	He/He' chemical shift <sup>a</sup>	4.37 ppm

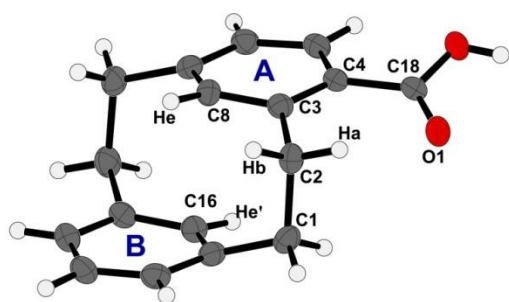
<sup>a</sup> in CDCl<sub>3</sub>

The X-ray structure confirmed the expected stepwise *anti* conformation typical of the [2.2]metacyclophane scaffold.<sup>14</sup> The characteristic geometrical feature of a strained metacyclophane is the out of plane bending of the aromatic rings into a boat conformation,<sup>5b</sup> represented for diester **6** with a deviation from planarity of 7.7(1)° and 7.7(4)° for A and B rings respectively (Table 1, entries 2 and 3). Its central ten-membered ring adopts a chair-like conformation, where the two aromatic rings sit in parallel planes as confirmed by the high <sup>1</sup>H NMR shielding of the two equivalent H<sub>e</sub> aromatic protons at 4.37 ppm (entry 10). Thus, the closest approach of the two benzene rings to one another is 2.66(1) Å, as measured from the C8 of A ring to the C16 of the other ring (entry 1). The bond length (1.574(2) Å) of the cavity measured from C1 to C2 (entry 4) together with the bond angle C1-C2-C3 of 109.94(12)° (entry 5) further confirm the shortness of the bridge and its effect on the ring strain and conformational rigidity of the molecular framework. Noteworthy is the orientation of the two carboxy methyl groups which adopt a co-planar conformation compared to the aromatic rings, with a torsion angle C3-C4-C18-O1 of −2.2(3)° for the A ring (entry 6) and C15-C14-C20-O3 of −9.5(2)° for the B ring (entry 7) respectively. The two carbonyl groups C18-O1 and C20-O3 are thus aligned facing to the bridge protons H<sub>a</sub> and H<sub>a'</sub>, which is confirmed in solution by <sup>1</sup>H NMR deshielding effect of 4.27 ppm for H<sub>a</sub>

and upfield shift of 1.96 ppm for H<sub>b</sub> (entries 8 and 9) compared to the more shielded H<sub>c</sub> and H<sub>d</sub> nuclei ( $\Delta\delta$  H<sub>c/d</sub> = 1.08 ppm) sited on the non-substituted face of the molecule.

The C-4 carboxylic substituted metacyclophane **8** was also crystallized at room temperature from an acetone solution into the triclinic space group *P*-1,<sup>15</sup> with a summary of the X-ray crystal and <sup>1</sup>H NMR data shown in Table 2.

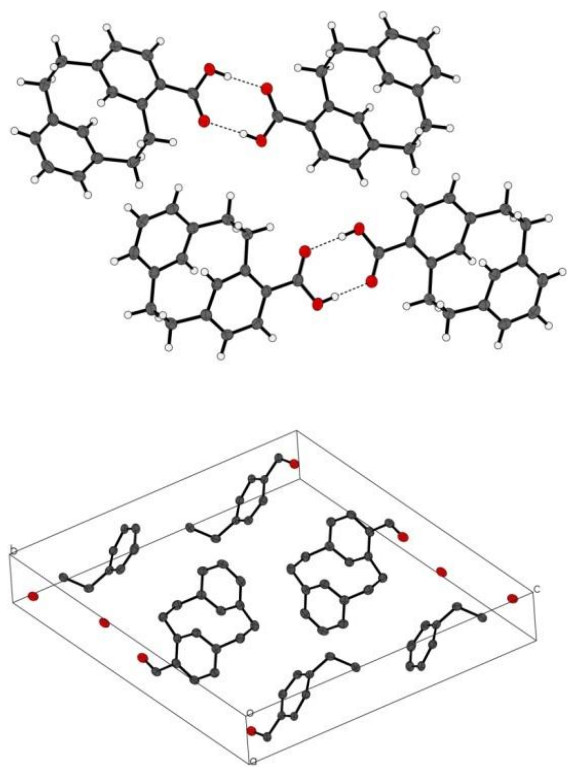
**Table 2:** Crystal Structure and relevant NMR data for **8**



Entry	Measurement	Data
1	Intra-annular distance (C8 to C16)	2.63(8) Å
2	A ring distortion from planarity	7.7(3)°
3	B ring distortion from planarity	7.2(4)°
4	Bond length C1-C2	1.569(3) Å
5	Angle C1-C2-C3	110.54(15)°
6	Torsion angle C3-C4-C18-O1	16.6(3)°
7	Ha chemical shift <sup>a</sup>	4.38 ppm
8	Hb chemical shift <sup>a</sup>	1.86 ppm
9	He chemical shift <sup>a</sup>	4.36 ppm
10	He' chemical shift <sup>a</sup>	4.33 ppm

<sup>a</sup> in CDCl<sub>3</sub>

The overall geometrical features of the metacyclophane **8** motif reflect the same architecture of the diester **6**, with a small ten-member ring cavity defined by a methylene bridge of 1.569(3) Å measured from C1 to C2, a bond angle of 110.54(15)° and the intra-annular distance of 2.63(8) Å (Table 2, entries 1, 4-5). The crystal structure shown again the parallel alignment of the two non-planar aromatic rings (entries 2 and 3) reflected in the  $^1\text{H}$  NMR shielding of the two non equivalent  $\text{H}_e$  and  $\text{H}_e'$  protons (entries 9 and 10). The carboxylic group has a small torsion angle of 16.6(3)° for C3-C4-C18-O1 (entry 6), causing an alignment of the CO group with the C2 bridge protons  $\text{H}_a$ . This could be attributed to the significant difference in chemical shift ( $\Delta\delta$  of 2.52 ppm) observed for equatorial  $\text{H}_a$  and axial  $\text{H}_b$   $^1\text{H}$  NMR signals (entries 7 and 8) in  $\text{CDCl}_3$ . The unit cell contains both enantiomers forming hydrogen bonded chains with a typical O–H length of 1.79(9) Å (Figure 2).

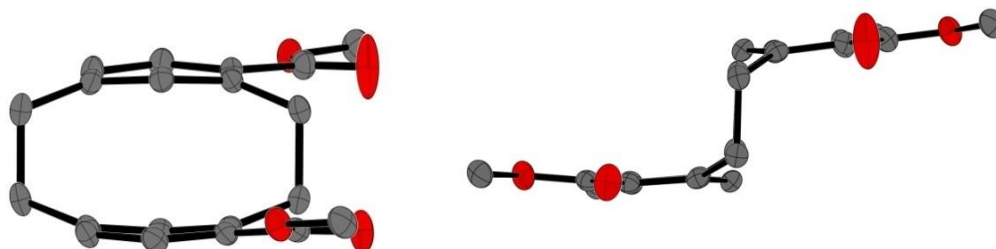


**Figure 2.** H-bonded chains (top) and unit cell (bottom) of X-ray structure **8**

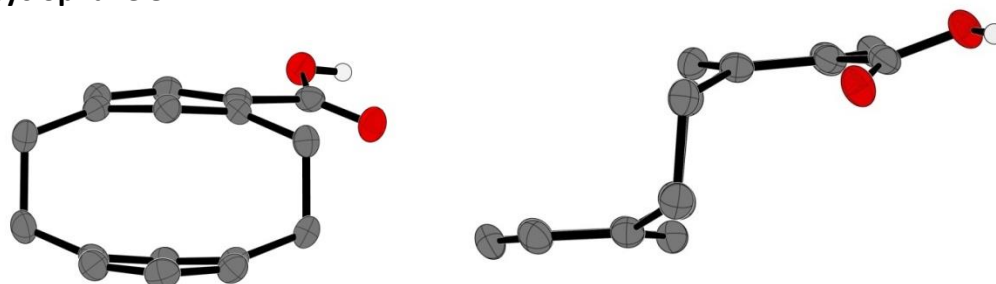
The spatial arrangement of the carboxylates groups into the 4- and 14- positions of the aryl rings is noteworthy, as the *anti* stepwise conformation of the metacyclophane scaffold presents the two

Bronsted acid functional groups in a unique manner. As shown in the frontal view of their X-ray structures, both derivatives **6** and **9** show a differentiation of the two sides of the molecules with respect to the vertical plane bisecting the metacyclophane ring (Figure 3, left). The carboxylate groups are pointing toward one side defining coordinating site(s) of the molecule, with the other side behaving as the chiral discriminator. Uniquely, the stepwise conformation may offer a potential chiral environment in an asymmetric transformation. Moreover, in the case of the disubstituted derivative **6**, the staggered conformation of the two aromatic rings arranges the functional groups into different planes (with a distance of 5.34 Å as measured from the two carbonyl sites), thus defining two potentially independent reactive sites on the same chiral scaffold (Figure 3, right).

#### Cyclophane **6**



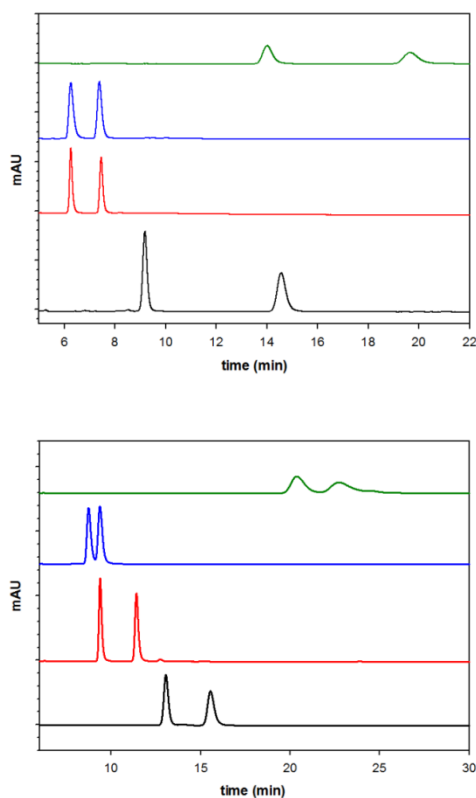
#### Cyclophane **8**



**Figure 3.** Front view (left) and side view (right) of X-ray structures **6** and **8**

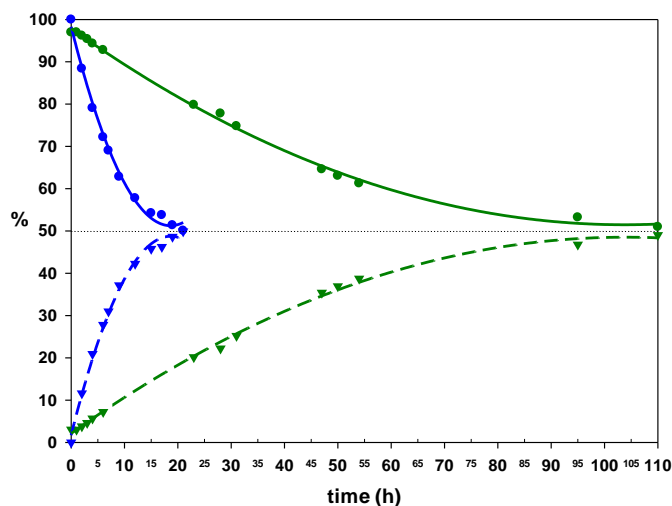
The racemic mixtures of methyl esters **6** and **9** were analyzed by analytical chiral HPLC under normal phase conditions, showing good to excellent separations on four different chiral stationary

phases (Figure 3). Racemates **6** and **9** were then resolved by semi-preparative chiral HPLC using a Chiralcel OD column, and the absolute configuration of pure enantiomers was assigned by comparison of the optical rotation with literature data.<sup>6b,12</sup>



**Figure 3.** Chiral HPLC separation of **6** (top) and **9** (bottom) over Chiralpak IA (black), Chiralpak IB (red), Chiralpak AS-H (blue) and Chiralcel OJ-H (green) columns.

Finally, enantiopure samples of esters **6** and **9** were subjected to racemization by heating in heptanes at 373 K or in *N*-methyl-2-pyrrolidone at 453 K and monitoring the course of the reaction by analytical chiral HPLC.



**Figure 4.** Racemization plots of esters **6** (blue) and **9** (green) in heptanes at 373 K.

Since the racemization process interconverts enantiomers *via* a reversible first-order reaction, the inversion barriers were calculated on the basis of the absolute rate equation<sup>16</sup> from the values of the rate constants determined *via* a first-order integrated law plot (Figure 4). From our racemization study on optically active cyclophanes **6** and **9** we found values for the inversion of the ten-membered ring of 31.1 kcal/mol and 32.3 kcal/mol respectively. Similar values (33.3 kcal/mol and 33.5 kcal/mol) were obtained in NMP at 453 K. Our racemization rates are consistent with those calculated in by Schlogl in 1974,<sup>5a</sup> confirming that while the inversion barriers are dependent on the length of the bridge,<sup>17</sup> the value is not affected by substituents on the aryl rings and therefore corresponds to the value of unsubstituted [2.2]metacyclophane scaffold.<sup>5b</sup> These values compare favorably with [2.2]paracyclophanes (37.8 kcal/mol) where the relatively high torsional barriers have been explained by a mechanism involving bond breaking to give achiral benzyl radicals as intermediates.<sup>18</sup>

## Conclusion

In summary a two step synthesis of the planar chiral [2.2]metacyclophane framework containing one or two carboxy functional groups at the key C-4/14 positions utilizing LiNK metalation and oxidative C-C bond formation has been described. The planar chiral derivatives have been characterized by X-ray crystallography and NMR, and the racemic mixtures separated by chiral HPLC. The ease of enantiomer separation and the relatively high inversion barrier to racemization indicates their potential as planar chiral catalysts and ligands which to date has not been explored.

## Experimental Details

**General Methods:** All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique. All solvents were purified and degassed before use. Chromatographic separations were carried out under pressure on Merck silica gel 60 using flash-column techniques. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel coated aluminum plates (60 Merck F254) with UV light (254 nm) as visualizing agent. Unless specified, all reagents were used as received without further purifications. TMP(H) was distilled from  $\text{CaH}_2$  prior to use and THF was obtained from a solvent purification system. BuLi was purchased as a 2.5 M solution in hexanes. KO $t$ -Bu was purchased as a 1 M solution in THF. The exact concentration of the organolithium solution was determined by titration with diphenylacetic acid in THF prior to use.<sup>19</sup>  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded at room temperature at 500 MHz and 100 or 125 MHz respectively and calibrated using residual undeuterated solvent as an internal reference.  $^2\text{H}$  NMR (92.07 MHz) spectra were obtained in DMSO using residual DMSO- $d_6$  as an internal standard. Compound **7** was synthesized as previously reported.<sup>9</sup> Optical rotations were measured at 589 nm. Analytical chiral HPLC analyses were performed on Daicel Chiralpak and Daicel Chiralcel series columns (250 x 4.6 mm ID) using heptane/ethanol as solvent mixtures. Semi-preparative HPLC analyses were carried out on a Daicel Chiralcel OD column (250 x 20 mm ID) using heptane/2-propanol as solvent mixtures.

**2,2'-(Ethane-1,2-diyl)bis(4-methylbenzoic acid) (3).**<sup>20</sup> A solution of 2,4-dimethylbenzoic acid **1** (451 mg, 3.00 mmol) in THF (15 mL) at  $-78^\circ\text{C}$  was treated dropwise with BuLi (2.40 M, 2.63 mL, 6.30 mmol) and stirred for 5 min. KO $t$ Bu (1.0 M in THF, 3.30 mL, 3.30 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.56 mL, 3.30 mmol). The reaction mixture was stirred for 15 min at  $-78^\circ\text{C}$  and 1,2-dibromoethane (0.77 mL, 9.00 mmol) added. The reaction mixture



was warmed to rt and the solvent removed under reduced pressure. Ethyl acetate (30 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Trituration from diethyl ether with cooling gave **3** as a white solid (367 mg, 82%), mp 287-288 °C (lit.<sup>20</sup> mp 289 °C). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 12.65 (bs, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.17-7.03 (m, 4H), 3.13 (s, 4H), 2.32 (s, 6H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ 169.0, 143.7, 142.1, 131.7, 131.0, 127.7, 127.1, 36.1, 21.4. HRMS [M-H]<sup>+</sup>: 297.1115, C<sub>18</sub>H<sub>17</sub>O<sub>4</sub> requires 297.1127.

**2,2'-(Ethane-1,2-diyl)bis(4-(deuteriomethyl)benzoic acid) (3-D<sub>2</sub>)**. A solution of 2,2'-(ethane-1,2-diyl)bis(4-methylbenzoic acid) **3** (60 mg, 0.20 mmol) in THF (10 mL) at -78 °C was treated dropwise with *n*BuLi (2.50 M, 0.33 mL, 0.82 mmol) and stirred for 5 min. KO<sup>t</sup>-Bu (1.0 M in THF, 0.42 mL, 0.42 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (71 μL, 0.42 mmol). The reaction mixture was stirred for 15 min at -78 °C and CD<sub>3</sub>OD (33 μL) added. The reaction mixture was warmed to rt and the solvent removed under reduced pressure. Ethyl acetate (20 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness to give **3-D<sub>2</sub>** as a white solid (51 mg, 84%; 80% D incorporation). <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>): δ 7.81-7.69 (m, 2H), 7.17-7.06 (m, 4H), 3.17-3.06 (m, 4H), 2.30 (s, 2H), 2.28 (s, 2H). <sup>13</sup>C NMR (125 MHz, DMSO-*d*<sub>6</sub>): δ 169.0, 143.7, 142.1, 131.7, 131.0, 127.7, 127.1, 36.1, 21.4 (t, *J* = 19.5 Hz). <sup>2</sup>H NMR (92.07 MHz, DMSO): δ 2.29 (s). HRMS [M]<sup>+</sup>: 300.1320, C<sub>18</sub>H<sub>16</sub>D<sub>2</sub>O<sub>4</sub> requires 300.1331.

**[2.2]Metacyclophane-4,14-dicarboxylic acid (5)**.<sup>11</sup> A solution of 2,2'-(ethane-1,2-diyl)bis(4-methylbenzoic acid) **3** (241 mg, 0.81 mmol) in THF (25 mL) at -78 °C was treated dropwise with BuLi (2.26 M, 1.47 mL, 3.32 mmol) and stirred for 5 min. KO<sup>t</sup>-Bu (1.0 M in THF, 1.70 mL, 1.70

mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.29 mL, 1.70 mmol). The reaction mixture was stirred for 30 min during which time the temperature was raised to  $-60\text{ }^{\circ}\text{C}$ . Afterwards 1,2-dibromoethane (0.16 mL, 2.43 mmol) was added, the reaction mixture was warmed to rt and the solvent was removed under reduced pressure. Diethyl ether (30 mL) was added to the residue and the diacid was extracted by aqueous NaOH (2 M, 20 mL). The basic solution was washed twice with diethyl ether and acidified to pH=1 with HCl (2 M, 40 mL). The diacid was then extracted with DCM (3 x 30 mL), the organic phase was dried over sodium sulphate and concentrated to dryness. Purification by filtration over a short silica gel plug eluting with 100:0 to 90:10 DCM:MeOH gave **5** as a white solid ( $R_f$  = 0.10, 83 mg, 35%), mp  $>350\text{ }^{\circ}\text{C}$ .  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  7.93 (d,  $J$  = 7.8 Hz, 2H), 7.16 (dd,  $J$  = 7.8, 1.4 Hz, 2H), 4.37-4.31 (m, 2H), 4.29-4.22 (m, 2H), 3.24-3.14 (m, 2H), 2.14-2.04 (m, 2H), 1.94-1.83 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CD}_3\text{OD}$ ):  $\delta$  169.9, 142.5, 140.3, 137.3, 131.3, 125.0 (2C), 40.1, 37.8. HRMS  $[\text{M}-\text{H}]^+$ : 295.0981,  $\text{C}_{18}\text{H}_{15}\text{O}_4$  requires 295.0970.

**[2.2]Metacyclophane-4,14-dicarboxylic acid dimethyl ester (6).**<sup>4c</sup> A solution of [2,2]metacyclophane-4,14-dicarboxylic acid **5** (47 mg, 0.16 mmol) in methanol (20 mL) was acidified with 12 M HCl (three drops) and heated under reflux for 16 h. The solvent was removed under reduced pressure and ethyl acetate (20 mL) was added. The organic layer was washed with saturated  $\text{NaHCO}_3$  and water, dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 80:20 cyclohexane:diethyl ether gave **6** as a white solid ( $R_f$  = 0.70, 4.9 mg), mp  $138\text{--}139\text{ }^{\circ}\text{C}$  (lit.<sup>4c</sup> mp  $138\text{--}140\text{ }^{\circ}\text{C}$ ).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d,  $J$  = 7.9 Hz, 2H), 7.13 (dd,  $J$  = 7.9, 1.6 Hz, 2H), 4.38-4.36 (m, 2H), 4.31-4.22 (m, 2H), 3.93 (s, 6H), 3.23-3.14 (m, 2H), 2.14-2.06 (m, 2H), 2.01-1.92 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  168.1, 142.4, 140.7, 137.7, 131.5, 126.6, 125.3, 51.9, 40.6, 38.2. HRMS  $[\text{M}+\text{H}]^+$ : 325.1456,  $\text{C}_{20}\text{H}_{21}\text{O}_4$

requires 325.1440.  $[\alpha]_D^{20} = +77.5$  (c 0.2, ethanol) and  $[\alpha]_D^{20} = -76.7$  (c 0.2, ethanol) after chiral semi-preparative HPLC. Analytical chiral HPLC analysis of the racemic mixture (254nm UV detector, room temperature, eluent: 2% ethanol in heptane, flow rate: 1.0 mL/min):

Daicel Chiralpak IA:  $t_1 = 9.2$  min and  $t_2 = 14.5$  min

Daicel Chiralpak IB:  $t_1 = 6.3$  min and  $t_2 = 7.4$  min

Daicel Chiralpak AS-H:  $t_1 = 6.3$  min and  $t_2 = 7.5$  min

Daicel Chiralcel OJ-H:  $t_1 = 14.0$  min and  $t_2 = 19.6$  min

**[2.2]Metacyclophane-4-carboxylic acid (8).**<sup>4a</sup> A solution of 4-methyl-2-(3-methylphenethyl)benzoic acid **7** (117 mg, 0.460 mmol) in THF (10 mL) at  $-78$  °C was treated dropwise with BuLi (2.50 M, 0.61 mL, 1.52 mmol) and stirred for 5 min. KO $t$ -Bu (1.0 M in THF, 1.01 mL, 1.01 mmol) was added dropwise followed by 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.01 mmol). The reaction mixture was stirred for 30 min during which time the temperature was raised to  $-60$  °C. Afterwards 1,2-dibromoethane (0.12 mL, 1.38 mmol) was added, the reaction mixture was warmed to rt and the solvent removed under reduced pressure. Ethyl acetate (20 mL) was added to the residue, washed with HCl (2 M, 3 x 10 mL), dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 1:1 cyclohexane:diethyl ether gave **8** as a white solid ( $R_f = 0.55$ , 46 mg, 39%), mp 192-196 °C (lit.<sup>4a</sup> mp 197-199 °C).  $^1\text{H}$  NMR (500 MHz, CD $_3$ OD):  $\delta$  7.83 (d,  $J = 7.9$  Hz, 1H), 7.21 (t,  $J = 7.5$  Hz, 1H), 7.06 (dd,  $J = 7.9, 1.4$  Hz, 1H), 7.06-6.92 (m, 2H), 4.21 (s, 1H), 4.18 (s, 1H), 4.15 (dt,  $J = 11.9, 3.6$  Hz, 1H), 3.09-3.04 (m, 2H), 3.01 (dt,  $J = 12.2, 3.6$  Hz, 1H), 2.10 (td,  $J = 12.2, 3.1$  Hz, 1H), 2.04-1.93 (m, 2H), 1.70 (td,  $J = 11.9, 3.1$  Hz, 1H).  $^{13}\text{C}$  NMR (125 MHz, CDCl $_3$ ):  $\delta$  172.0, 144.4, 141.4, 139.3, 138.6, 138.6, 138.1, 135.8, 132.2, 129.3, 125.8, 125.6, 125.3, 41.0, 40.7, 40.3, 39.2. HRMS  $[\text{M}-\text{H}]^+$ : 251.1078, C $_{17}\text{H}_{15}\text{O}_2$  requires 251.1072.

**[2.2]Metacyclophane-4-carboxylic acid methyl ester (9).**<sup>4a</sup> A solution of [2,2]metacyclophane-4-carboxylic acid **8** (22 mg, 0.09 mmol) in methanol (10 mL) was acidified with 12 M HCl (three drops) and heated under reflux for 16 h. The solvent was removed under reduced pressure and ethyl acetate (20 mL) was added. The organic layer was washed with saturated NaHCO<sub>3</sub> and water, dried over sodium sulphate and concentrated to dryness. Purification by silica gel chromatography eluting with 90:10 cyclohexane:ethyl acetate gave **9** as a white solid (*R*<sub>f</sub> = 0.80, 18 mg, 75%), mp 68-70 °C (lit.<sup>4a</sup> mp 71-73 °C). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.92 (d, *J* = 7.9 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.13-7.04 (m, 3H), 4.32 (s, 1H), 4.30 (s, 1H), 4.22 (dt, *J* = 11.9, 3.6 Hz, 1H), 3.92 (s, 3H), 3.19-3.10 (m, 3H), 2.24 (td, *J* = 12.3, 3.2 Hz, 1H), 2.15-2.05 (m, 2H), 1.84 (td, *J* = 11.9, 3.3 Hz, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): 168.1, 143.3, 140.5, 139.3, 138.4, 138.1, 135.9, 131.1, 129.2, 126.2, 125.8, 125.4, 125.3, 51.8, 40.9, 40.7, 40.2, 39.0. HRMS [*M*]<sup>+</sup>: 266.1299, C<sub>18</sub>H<sub>18</sub>O<sub>2</sub> requires 266.1307. [*α*]<sub>D</sub><sup>20</sup> = +5.5 (c 0.5, CHCl<sub>3</sub>) and [*α*]<sub>D</sub><sup>20</sup> = -6.0 (c 0.5, CHCl<sub>3</sub>) after chiral semi-preparative HPLC. Analytical chiral HPLC analysis of the racemic mixture (254nm UV detector, room temperature, eluent: 0.2% ethanol in heptane, flow rate: 0.7 mL/min):

Daicel Chiralpak IA: *t*<sub>1</sub> = 13.0 min and *t*<sub>2</sub> = 15.5 min

Daicel Chiralpak IB: *t*<sub>1</sub> = 9.4 min and *t*<sub>2</sub> = 11.4 min

Daicel Chiralpak AS-H: *t*<sub>1</sub> = 8.7 min and *t*<sub>2</sub> = 9.3 min

Daicel Chiralcel OJ-H: *t*<sub>1</sub> = 20.3 min and *t*<sub>2</sub> = 22.7 min

**General procedure for the racemization of [2.2]metacyclophanes (heptane).** In a round-bottom flask equipped with a reflux condenser, a sample of enantiopure [2.2]metacyclophane (0.5 mg) was dissolved in heptane (1 mL) and heated at reflux (373 K). At a specified time interval, a sample of 20 μL was taken and directly submitted for HPLC analysis.

**General procedure for the racemization of [2.2]metacyclophanes (NMP).** In a round-bottom flask equipped with a reflux condenser, a sample of enantiopure [2.2]metacyclophane (0.5 mg) was dissolved in *N*-methyl-2-pyrrolidone (1 mL) and heated at 453 K. At a specified time interval, a sample (approx. vol. 100  $\mu$ L) was taken and rapidly cooled to room temperature with an ice bath. Heptane (approx. vol. 0.5 mL) was added and, after a short micro extraction, the upper heptane layer was isolated and submitted for HPLC analysis.

## Supporting Information

$^1\text{H}$ ,  $^2\text{H}$  and  $^{13}\text{C}$  NMR spectra for compounds **3**, **3-D<sub>2</sub>**, **5**, **6**, **8** and **9**. X-Ray crystallographic data for **6** and **8**. Chiral semi-preparative HPLC resolution plots of **6** and **9** and racemization plots data.

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